1045-Plat
Studying the Gating Mechanism of Mammalian Kir Channels using in Silico Mutations
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Inward rectifier potassium (Kir) channels are essential membrane proteins, controlling the permeation of K^+ ions across membranes. They are found in eukaryotes as well as bacteria. These channels are expressed in multiple tissues and responsible for a wide range of physiological processes i.e. shaping the action potential, insulin decrease and neurotransmitter response. Crystal structures have provided major insights into the architecture of these channels. So far, all mammalian structures have been captured in a closed state. Recently, the first putative open structure of a bacterial Kir channel was obtained using a gating mutant (S129R) close to the helix bundle crossing region (HBC) (Bavro et al., 2012). Thus, we reasoned that introducing such a mutant in a mammalian Kir channel might enable investigating the open state.
Therefore, we introduced in silico mutations in all for subunits at gating sensitive regions and conducted up to 1μs molecular dynamics simulations.
Intriguingly, during the mutant simulations major conformational changes were observed. In all simulations, widening at the HBC gate occurred. These changes enabled continuous water flux through this gate and access for hydrated potassium ions to the cavity. A major difference to native mammalian Kir channels is the PIP2 dependence. In contrast to the wild type channels, our charged mutant channels do not need PIP2 to induce opening. This is likely due to the strong repulsive effects of the negative charges. Importantly, changes in the lipid interactions of the slide helix reveal a movement of this helix towards the lipid head groups during opening, in agreement with experimentally observed lipid interaction changes (Lee et al., 2013).
It cannot be excluded that mutant channels stabilize rarely populated open states, as previously reported for selected bacterial Kir channel mutants (Zubcevic et al. 2014).

1046-Plat
Multiscale Analysis of Functional Motions in F1-ATPase: From Pi Release to Elasticity and Friction of γ-Subunit Rotation
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F1-ATPase, the catalytic domain of ATP synthase, synthesizes most of the ATP in living organisms. Running in reverse powered by ATP hydrolysis, this hexameric ring-shaped molecular motor formed by three αβ-dimers creates torque on its central γ-subunit. This reverse operation enables detailed explorations of the mechano-chemical coupling mechanisms in experiment and simulation. First, we use molecular dynamics (MD) simulations to construct an atomistic conformation of the intermediate state following the 40° substep of rotary motion, and to study the timing and molecular mechanism of inorganic phosphate (Pi) release coupled to the rotation. In response to torque-driven rotation of the γ-subunit in the hydrolysis direction, the nucleotide-free αβE interface forming the ''empty'' E site loosens and singly charged Pi readily escapes to the P-loop. The γ-rotation tightens the ATP-bound αβTP interface, as required for hydrolysis. On the basis of metadynamics simulations and rate calculations, we then clarify the timing and pathway of Pi release [1]. Second, from the MD simulation trajectories we introduce a simple model to estimate the elastic properties of the central γ-subunit and the friction affecting γ-subunit rotation. The estimated elastic properties are consistent with experiments. According to our analysis, the work performed in the torque-driven rotation is mostly stored as elastic energy with remarkably little dissipation even at high angular velocities. We also estimate the maximum rotational speed without load, which is not available in experiments.
[1] Okazaki and Hummer PNAS 110:41 (2013) 16468-16473

1047-Plat
Ion Channel Regulation by Lipid Bilayers: Theory & Simulation of Deformed Membranes around Gramicidin A
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The energetic coupling between an integral membrane protein and its host bilayer depends on the protein structure and the bilayer material properties (e.g., hydrophobic thickness, intrinsic lipid curvature, compression modulus, and bending modulus). Therefore, if a bilayer is modulated by a membrane protein conformational change, the energetics of the protein-induced bilayer deformations must be considered. To explore this energetic coupling, gramicidin A (gA) monomer↔dimer association was used as a surrogate for conformational transitions of large membrane proteins that perturb the host bilayer. gA channels provide similar physics of bilayer modulation since they form by transmembrane dimerization, and deform the bilayer to match the hydrophobic length of the channel. gA channels were simulated in five single-component bilayers formed of mono-unsaturated lipids with increasing chain length, leading to thicker bilayers, and increased deformation around the peptide. These deformations are analyzed primarily in terms of compression (i.e., placing a tall lipid next to the shorter channel) and bending. Lipid compression and bending both cause bilayer stresses, and these stresses lead to curvature frustration of the individual leaflets. The per area free energy of bending with respect to curvature, dF/dR^{-1}, (a sensitive measure of bilayer stress) is calculated and compared to the predictions based on a continuum elastic model (CEM). It is shown that gA monomer insertion produces similar contributions to dF/dR^{-1} independent of bilayer type, and gA dimerization increases dF/dR^{-1} systematically with bilayer thickness. The increase in dF/dR^{-1} is indicative of increased bilayer stresses due to dimerization. In tandem with the CEM results, the all-atom values allow for development of an improved CEM, and determination of the compression and bending energies that can be compared to experiment.

1048-Plat
Atomistic Characterization of the HIV Capsid from Molecular Dynamics Simulations
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The HIV capsid is large, containing about 1,300 proteins with altogether 4 million atoms. Although the capsid proteins are all identical, they nevertheless arrange themselves into a largely asymmetric structure. The large size and lack of symmetry pose a huge challenge to studying the chemical details of the HIV capsid. Simulations of 64 million atoms for over 1 micro- second allow us to conduct a comprehensive study of the physical properties of the entire HIV capsid including electrostatic potential, all-atom normal modes, as well as the effects of the solvent (ions and water) on the capsid. The results from the simulations reveal critical details of the capsid protein with important implications for assembly, uncoating and nuclear import.

Awards and National Lecture

1049-Natl
Discoveries in Biophysics through the Computational Microscope
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All-atom molecular dynamics simulations resolve the physical mechanisms underlying the dynamic function of biological macromolecules and serve today as a computational microscope. This microscope truly complements and goes hand-in-hand with experimental observation, though it has also made its own discoveries, for example, in studies of protein mechanics. Progress in developing the computational microscope was tied to advances in the size and time scale covered by molecular dynamics simulations: reaching the 100,000 atom and 10-ns scales in 2000 opened the field of *in situ* membrane protein simulations leading to the discovery of selectivity and gating in water and ion channels; reaching the million atom and μs-to-ms scales in 2010 resolved the actual folding pathways of 50-100 aa long proteins and of the control mechanisms in the ribosome, including the insertion of nascent proteins into a membrane. Recently, simulations have reached the 100 million atom and μs-to-ms scales permitting, in conjunction with multi-modal structural biology experiments, atomic-level images of the HIV capsid and its chemical interaction with host cell factors. Simulations now permit even the electronic-to-atomic level description of an entire photosynthetic membrane through a combination of various experiments with molecular dynamics simulations, quantum mechanical calculations and kinetic modeling. Culminating over four decades of investigation, the results have led to an atomic-level model of a spherical membrane, the photosynthetic chromatophore of purple bacteria, made of 20,000 lipids and 100 proteins with 3,000 co-factors. A movie based on the model reveals the step-by-step electronic- and atomic-level conversion of light energy into ATP synthesis. The lecture illustrates also the many-fold algorithmic advances in sampling, force evaluation, physical analysis, automated model construction, molecular graphics and experimental data analysis that were necessary to reach the present stage of computational microscopy.